Risk factors for cardiovascular disease and hormone therapy in women

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Cardiovascular disease (CVD) results in substantial morbidity and mortality in most western countries in the world. The mortality burden of CVD in the UK in 2002 appears to be similar in men and women and CVD accounts for approximately 39.1% of deaths in men and 39.2% in women (http://www.heartstats.org/). Rates for coronary heart disease (CHD) mortality in the UK have been falling since 1970. CHD is a multifactorial disease, but certain major risk factors can account for the vast majority of acute myocardial infarction (MI). A recently published study (INTERHEART) of nearly 30 000 men and women from different communities and ethnic groups worldwide showed that such risk factors are common to all groups and can predict over 90% of the CHD risk. Lifestyle factors, including cigarette smoking, poor diet high in saturated fats and low in fruit and vegetables, physical inactivity, and stress have an important causal role in the incidence of CHD in all populations, while moderate alcohol consumption is protective.[1] Genetic and environmental factors are also significant. Metabolic diseases and risk factors, including diabetes mellitus, obesity, dyslipidaemia, hypertension, and insulin resistance, have a substantial impact on the development of CHD. These risk factors contribute to the development of atherosclerosis and thrombotic complications. Reducing these risk factors can slow the progression of CHD and its clinical complications before, and even after, the occurrence of a cardiovascular event.

Loss of ovarian hormones at the menopause has a widespread adverse impact on many of these risk factors. However, recent large clinical trials of essentially one form of hormone therapy (HT) have not shown a benefit on cardiovascular risk and therefore, at the present time, HT is not recommended in postmenopausal women solely for cardioprotection. The failure of the clinical trials to show a benefit may be, in part, due to the selection of the wrong population in terms of age, but may additionally be due to inappropriate HT regimens, in terms of dose and possibly type of steroids, being employed. A pattern of early harm followed by later benefit has emerged from these trials. It is plausible that transient adverse effects on thrombogenesis and vascular remodelling are responsible for the early harm, while beneficial effects on metabolic risk factors and arterial function are responsible for the later benefit. HT regimens vary considerably in their metabolic effects, and hence in their cardiovascular effects. Further research is required to define the ideal dose, type, route of administration, and duration of HT for maximum potential cardiovascular benefit. These aspects will be discussed further.

RISK FACTORS FOR CHD

Risk factors can be modifiable, potentially modifiable, or fixed. Definitely modifiable factors include; blood lipids, blood pressure, cigarette smoking, lifestyle and behavioural factors. Potentially modifiable risk factors include newer parameters such as homocysteine and hs C-reactive protein (CRP). The scientific information for these factors is generally less certain than for the definitely modifiable factors. The fixed risk factors for CHD include age, gender, and family history. Genetics may contribute to each of these groupings and alter CHD risk. For example, familial hypercholesterolaemia, a genetic disorder, is now considered a definitely modifiable condition, and modern lipid lowering therapy can reduce CHD risk in these individuals. The lifetime risk for CHD is highly related to age and gender. The lifetime risks for CHD in women are lower at each age in comparison to men. Overall, the lifetime risk for CHD is approximately 40% in men and 30% in women.[2] In contrast, the lifetime risk for developing breast cancer in women is approximately 10%, a rate that is much lower than a woman's lifetime risk for CHD. In a follow up of this study the lifetime risks were also related to total cholesterol value in both sexes and a higher cholesterol value at age 40–49 led to greater risk of CHD.[3]

AGE

CHD in women tends to occur after menopause, and rates are significantly higher than for other common diseases of ageing, including fractures, cerebrovascular disease, breast cancer, and uterine cancer.[4] In general risk factor levels increase with age, though they level off at older ages. These cross sectional patterns reflect not only the influence of age on risk factors, but may also be affected by selective survival (men with high levels of risk factors are more likely to die at younger ages).

CIGARETTE SMOKING

The prevalence of cigarette smoking has declined in a large number of western countries but it is increasing in Asia. Cigarette smoking generally trebles the risk of CHD outcomes.[1] Both regular and filter cigarettes have similar adverse effects on CHD risk.[5] Cessation of cigarette smoking was associated with half the risk for CVD death in 1–2 years after quitting in men screened as part of the MRFIT study (Multiple Risk Factor Intervention Trial), and the effects for smoking cessation on the clinical course of CHD risk in women were similar.[6]

LIPIDS

Higher concentrations of cholesterol are related to the development of CHD, and the evidence for the major importance of raised blood cholesterol for CHD in both men and women is now overwhelming. In women the greater CHD risk is typically not observed before menopause, even if

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high density lipoprotein; HERS, Heart & Estrogen Replacement Study; HT, hormone therapy; KEEPS, Kronos early estrogen prevention study; LDL, low density lipoprotein; Lp(a), lipoprotein (a); MI, myocardial infarction; MPA, medroxyprogesterone acetate; MRFIT, Multiple Risk Factor Intervention Trial; NETA, norethisterone acetate; WHI, Women's Health Initiative

cholesterol concentrations are quite elevated. Using a cholesterol concentration of 5.17 mmol/l (200 mg/dl) as the comparison, a value of 6.46 mmol/l (250 mg/dl) has typically led to a twofold risk of CHD death, and a value of 7.75 mmol/l (300 mg/dl) led to a threefold risk of CHD death; these relative risk effects are similar in men and women.[7]

High density lipoprotein (HDL) cholesterol is a major fraction of cholesterol in the plasma and is an important determinant of risk for CHD and MI, even when the total cholesterol value is known. The 12 year incidence of MI was positively related to the cholesterol concentration and inversely related to the HDL cholesterol concentration in women in the Framingham study.[8] At a total cholesterol concentration $<$ 5.45 mmol/l (211 mg/dl) the HDL cholesterol values were inversely related to risk of developing MI in these women. The total/HDL cholesterol ratio is another way to represent the relation between these simple lipid measures and CHD risk, which is highly related to this ratio. Total cholesterol and low density lipoprotein (LDL) cholesterol had similar predictive capabilities in the prediction of CHD in women in multivariate models that also included age and HDL cholesterol, suggesting that total cholesterol is adequate for screening purposes at a population level.[9]

Lipoprotein (a) (Lp(a)) is an accepted determinant of CHD risk, and routine screening for Lp(a) values has been recommended for persons with premature CHD that is not explained by conventional risk factor levels.[10 11]

A recent meta-analysis suggested that current evidence was still insufficient to determine conclusively whether drug treatment of hyperlipidaemia may reduce CHD events in women without known CVD.[12] Assuming a 20% reduction in CHD with treatment of hypercholesterolaemia in all age and sex groups, the estimated number of women needing to be treated to prevent one coronary event within five years is greater than for men the same age.[13]

BLOOD PRESSURE

Risk of CHD is highly related to blood pressure level and levels of systolic pressure are typically more highly associated with the development of clinical disease than levels of diastolic blood pressure. Systolic and diastolic hypertension generally confer a relative risk of 1.6 for CHD; for combined systolic and diastolic hypertension the relative risk is 2.0.[14 15] Pulse pressure is also related to CVD outcomes, especially in older men and women, as diastolic pressures typically are lower in the elderly than those observed in middle age.[16]

A large review of observational studies of blood pressure suggested that at age 40–69 years a difference of 20 mm Hg in systolic pressure or 10 mm Hg in diastolic pressure is related to approximately a twofold difference in death rate from ischaemic heart disease.[17]

OBESITY AND HEART DISEASE

Excess adiposity has been defined by the World Health Organization, using body mass index (BMI = body weight in kilograms divided by height in metres squared) and abdominal girth (greatest circumference of the abdomen when a subject is standing). Using these measures, overweight is present for a BMI 25–29.9 kg/m^2 and obesity for a BMI $>$ 30 kg/m^2. Increased abdominal adiposity is defined as $>$ 90 cm for women and $>$ 100 cm for men.

In England about 43% of men and 34% of women are overweight (BMI of 25–30 kg/m^2) and an additional 22% of men and 23% of women are obese (BMI of $>$ 30 kg/m^2). Central obesity is also common with 28% of men and 20% of women with central obesity constituting the insulin resistance syndrome, a risk factor for CHD

The risk of having an MI increases proportionately to BMI. Mortality rates clearly rise in proportion to degree of obesity,[18] explained in large part by the multiple co-morbid conditions which are associated with CVD: hypertension, dyslipidaemia, type 2 diabetes, coronary artery disease, stroke, sleep apnoea, and congestive heart failure. Insulin resistance, which includes a disease spectrum ranging from impaired glucose tolerance and the metabolic syndrome, to overt type 2 diabetes mellitus, appears to be even more common among the obese than hypertension[19] Obesity results in an increase in bioactive molecules termed adipocytokines which can lead to an increase in atherosclerosis as they are associated with inflammation, and therefore obesity can be considered an independent risk factor for CVD.[20]

Alcohol intake has consistently been related to a reduced risk of CHD, and an intake in the range of more than two drinks a day in men and more than one drink a day in women appears to confer this benefit.[21–23] Favourable effects on HDL cholesterol concentrations are thought to be important in exerting this effect, as well as anti-inflammatory and antiplatelet actions.

LIFESTYLE RISK FACTORS

A plethora of lifestyle factors are implicated in CHD which can be broadly classified as dietary, physical activity, and psychosocial. Some of these may have effects through influencing levels of known physiological risk factors such as lipid concentrations, blood pressure and fibrinogen, but others may have effects through other mechanisms involved in atherosclerosis and thrombosis. As with the physiological risk factors, it is important to note that much of the evidence is based on men only, though it may seem reasonable to assume here too that many of the biological effects may be similar in men and women. There are virtually no randomised trials of primary prevention of CHD using lifestyle measures in women. Some secondary prevention trials have included women, though these have all had insufficient numbers and inadequate power to examine results in women separately.

PHYSICAL ACTIVITY

Subjects with a more active lifestyle generally experience lower risk for CHD. Early studies investigated occupations and risk for CHD, but more recent research has concentrated on leisure time physical activity. There are strong empirical data for the prescription of 30 minutes per day of moderate intensity activity. A study from the United States assessed 73 743 postmenopausal women aged 50–79 years participating in the Women's Health Initiative, showing that walking briskly for at least 2.5 hours per week (that is, 30 minutes five times per week) was associated with a 30% reduction in cardiovascular events over 3.2 years of follow up.[24] After adjustment for total exercise energy expenditure, brisk walking and more vigorous exercise were associated with similar risk reductions in cardiovascular events, and the results did not vary substantially according to race, age, or baseline body mass index.

The cardiovascular benefits of walking have also been demonstrated in other studies of middle-aged and older women. In the Nurses' Health Study, an eight year follow-up of 72 488 healthy female nurses aged 40–65 years, three hours of brisk walking per week had the same protective effect as 1.5 hours of vigorous exercise per week.[25] Women engaging in either form of exercise had a 30–40% lower rate of MI than sedentary women. In the Women's Health Study, which followed 39 372 healthy middle-aged female health professionals for seven years, walking at least one hour per week was associated with a 50% reduction in CHD risk in individuals reporting no vigorous physical activity.[26] Among 1564 middle-aged women followed for 30 years, walking moderately every day as compared with walking minimally

every day was associated with a 33% reduction in CVD incidence.[27] In the Study of Osteoporotic Fractures, a 10 year follow-up of 9704 women aged 65 years or older, participants with weekly walking energy expenditures averaging 300 kcal or more (that is, about ⩾ 1 hour of walking per week) experienced an approximate 34% reduction in CVD mortality as compared with those with weekly walking energy expenditures below 70 kcal.[28]

DIABETES MELLITUS

In the United Kingdom, diabetes is slightly more common in women (17.7%) than men (13.4%) at all ages,[29] although rates may be higher in ethnic minorities in whom diabetes is more common. Diabetes increases the risk of CHD in both sexes, 2.5-fold in men and over fourfold in women.[1] With the increasing incidence of obesity there is a parallel increase in the prevalence of type 2 diabetes. The prevalence of type 2 diabetes mellitus rises with age in both sexes and at age 50 years approximately 4% of the population is affected. Data from Finland and the INTERHEART study suggests that the risk for an MI in a subject with diabetes is very similar to the risk for persons who have had an MI and is at risk for a subsequent event. Type 2 diabetes mellitus is therefore considered a CHD risk equivalent, and aggressive treatment of risk factors in persons with type 2 diabetes mellitus to prevent CHD events is justified.[1 30]

Aggressive risk reduction in diabetics is now recommended especially with regard to LDL cholesterol and blood pressure.[31 32] The success of such an approach has been demonstrated in both men and women with type 2 diabetes involving aggressive treatment for hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria.[33]

SEX HORMONES

Men and women obviously differ in endogenous sex hormone concentrations and a general assumption has been that women have less CHD than men because either high oestrogen values are protective or high testosterone values adverse for CHD.

While increased CHD risk in women who have an early menopause has been reported,[34] prospective studies have found no relation between measured endogenous oestrogen or testosterone and CHD in women.[35] Conversely, studies examining endogenous testosterone concentrations in men have found no consistent significant relations with CHD or risk factors; if anything, the associations with endogenous testosterone concentrations appear to be in a beneficial direction.[36]

HORMONES AND CVD

Almost all epidemiological studies have indicated a beneficial effect of HT on the risk and development of CHD in postmenopausal women. Randomised trials using hard clinical end points have failed to show a significant reduction in coronary events from HT use. A pattern of early harm followed by later benefit has emerged from these trials. It is plausible that transient adverse effects on thrombogenesis and vascular remodelling are responsible for the early harm, while beneficial effects on metabolic risk factors and arterial function are responsible for the later benefit. It must be appreciated that HT regimens vary considerably in their metabolic effects, and hence in their cardiovascular effects. Further research is urgently required to define the ideal dose, type, route of administration, and duration of HT for maximum cardiovascular benefit. HT is licensed and used for relief of menopausal symptoms and the prevention of postmenopausal osteoporosis. At present, there is insufficient evidence to justify using HT solely for the prevention and treatment of CHD in postmenopausal women.[37]

CLINICAL END POINT STUDIES

The HERS prospective clinical trial of HT enrolled 2763 postmenopausal women, mean age 67 years, with established CHD who were randomised to receive conjugated equine oestrogens 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo.[38] After a mean of four years of follow-up there was no significant difference between the groups in the outcomes of non-fatal MI or cardiac death. Interpretation of these data is complex. In the first year after randomisation patients in the HT group had an increased event rate that decreased steadily in the subsequent years, with a significant trend (post-hoc analysis). In the placebo group, the event rate was lower than expected in the first year, with higher rates during further follow-up. It remains unknown if these observations reflect a true pattern of events, or whether such variations may be due to chance. There was in fact an imbalance in the use of statins between the groups, with greater usage in the placebo group. Another major concern about trials of older postmenopausal women is the starting dose of HT used.[39]

This pattern of early increase and late decrease in CHD risk seen in HERS has been seen in other secondary prevention studies of HT. The small PHASE randomised trial of transdermal oestradiol 17β with or without transdermal NETA also failed to show benefit in women with CHD,[40] but again the dose of oestradiol used (80 μg/day) was high for the age of the patients. In contrast, a randomised trial using the relatively lower dose of oral oestradiol 1 mg daily showed a non-significant reduction in coronary deaths during the first 12 months of study, although no breakdown of coronary events was given.[41]

The Women's Health Initiative trials of HT for primary prevention of CHD were conducted in healthy postmenopausal women aged between 50–80 years. Non-hysterectomised women (16 608) were randomised to either conjugated equine estrogens 0.625 mg plus MPA 2.5 mg daily or placebo, and followed for a mean duration of 5.2 years.[42] Hysterectomised women (10739 subjects) were randomised to either conjugated equine estrogens 0.625 mg daily alone or placebo, and followed for a mean duration of 6.8 years.[43] These trials also showed an early increase in clinical coronary events followed by a subsequent decline. Exactly the same oestrogen doses were used in these trials in women aged up to 80 years as were used in HERS, ERA and WAVE.

A common finding of these clinical trials of HT is an apparent increase in cardiovascular events in the HT group in the early years of treatment, which appears to diminish in later years. One possible explanation for this observation of ''early harm'' is an increase in thrombogenesis, which would be immediate on commencement of the therapy but would also be transient as the haemostatic system of coagulation and fibrinolysis came back into balance. This effect on thrombogenesis would be dose dependent. Many researchers in the field have criticised these studies for giving relatively high doses of hormones to relatively elderly women with or at risk of CVD. There is good rationale for lower doses of hormones started earlier before the disease process has become too advanced.

CONCLUSIONS

Women have consistently lower CHD rates than men. The classical risk factors—blood pressure, raised blood cholesterol, and cigarette smoking—appear to confer the same relative increase in CHD risk in women, and some of the sex difference in CHD can be explained by lower levels of risk factors in women, at least at younger ages. In particular, cigarette smoking has been substantially less in the past in women compared to men, but trends appear to be reversing in younger women. Some of the apparent protection that

women seem to have from CHD may diminish as prevalence of cigarette smoking in women increases and even exceeds that in men.

The absolute risk of CHD at any age, even after adjusting for risk factors, is about two to three times greater in men. This has implications for individual based preventive interventions such as pharmacologic treatment of hypertension and hypercholesterolaemia. Even if these confer similar relative benefits for CHD in men and women, the absolute benefit is likely to be lower in women. Thus, the risk-benefit balance may be different and more finely balanced in women compared to men when individual preventive treatments are considered.

Hormone therapy and CVD

As indicated, this is a complex and evolving area. At present, there is insufficient evidence to justify using hormone therapy solely for the prevention and treatment of CHD in postmenopausal women.[44] Many large epidemiological studies in the field demonstrate a powerful protective effect of HT on CVD events. Why this inconsistency with the clinical trials? A number of confounding factors can play a role in observational studies such as the ''healthy user'' bias and inability to detect early harm. One other important difference is that in the observational studies HT has been started at a younger age and for different clinical indications—that is, peri-or post-menopausal symptoms. The data from clinical trials of HT are therefore limited by the populations of women that have been investigated—that is, more elderly women with increased progression of disease rather than younger peri-menopausal women where prevention may stand a greater chance of success. We should therefore still be guarded about generalising that all HT will not benefit the cardiovascular system at any time. There are serious questions regarding the choice of HT preparations, different oestrogen and progestin combinations and doses (lower), and perhaps more important the age at which women are exposed to these agents. An ideal comparative example would be the evaluation of the cardioprotective effect of a statin in more elderly women at risk of CVD where a standard dose of pravastatin (which clearly reduced CV risk in men) had no such effect women (the PROSPER study)[45]; these results were almost identical to the first randomised HT study, the HERS study.[38] If PROSPER were the first clinical trial of a statin in elderly women for cardioprotection we may be making the same conclusions that statins should not be used for the sole purpose of cardioprotection in this population. This reinforces the fact that women may respond differently; what is clearly needed is more research in this area particularly in female populations. With regard to HT what ideally is required is the investigation of different and lower doses of HT in younger women who are at risk of CVD, before complex atheromatous lesions have developed.[46] Some attempts are being made to address these issues, albeit investigating surrogate CV end points rather than hard end points, in studies such as the KEEPS (Kronos early estrogen prevention study) which began in mid 2005 investigating recently menopausal women and the effect of HT on CV risk factors and surrogate end points for atherosclerosis.[47]

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